REMARKS

Status of the Application.

Claims 1, 19, 28, 30-31, and 33-50 are pending in the application. Applicants reserve the right to file further continuation applications on any subject matter disclosed in the instant application or on the subject matter of any previously or presently cancelled claim. Claims 1, 19, 28, 30, 39, 42 and 49 have been amended herein. Claims 1, 28, 39 and 42 have been amended to more clearly state the metes and bounds of the claim. Claims 19, 28 and 30 have been amended to correct typographical errors. Claim 49 has been amended to clarify the claim without altering the scope thereof. Applicants assert new matter has not been introduced by the amendment.

Claim Objections.

Claims 1 and 28 are objected to as grammatically incorrect as reciting "the residue position corresponding to sites" or "the residue positions corresponding to site". Applicants respectfully point out the claim 1 in the previous amendment had removed the "s" from "sites". Similarly, claim 28 had been amended to remove the "s" from "positions". Applicants do acknowledge that the strikethrough was difficult to see however Applicants believe no further correction is needed. Withdrawal of the objection is respectfully requested.

Claims 28 and 30 are objected to as reciting "SEQ ID NO:-2". Applicants have amended the claims to remove the improper sequence identifier. Withdrawal of the objection is respectfully requested.

35 U.S.C. §112, first paragraph.

Claims 1, 19, 31, 34-41, 44 and 46-50

Claims 1, 19, 31, 34-41, 44 and 46-50 stand rejected under 35 USC §112, first paragraph as failing to be described in the specification. Specifically, the Examiner asserts that the specification, claims or drawings as originally filed fail to describe a variant that has a mutation at either position 192 (Claim 1 and claims dependent thereform) or position 194 (Claim 39 and claims dependent therefrom) as having increased polyesterase activity and enhanced

thermostability. Emphasis in original; see page 5 of the Office Action. Applicant respectfully traverses.

Initially, Applicants once again note that SEQ ID NO:2 contains a leader peptide and is numbered beginning at the initiating methionine. The mature sequence, after cleavage of the leader peptide (14 amino acid residues) begins at the alanine in position 15 (*i.e.*, Ala 15 represents the first residue in the protein). Therefore, Phe 180 in the Claims refers to Phe 194 in Figure 18 and SEQ ID NO:2. Thus, the Examiner may be looking for 194 in the specification but should be looking for 180. If the Examiner would find a substitute Sequence Listing to be helpful, Applicants would be happy to provide a new Sequence Listing that includes a sequence that omits the leader peptide.

Applicants have amended Claim 1 to more clearly describe what is considered the invention. The currently pending claim now requires increased polyesterase activity and/or enhanced thermostability. Support for this can be found, for example, in Tables 1 and 3 where variants having a substitution at residue 192 show an increased polyesterase activity and both increased polyesterase activity and enhanced thermostability, respectively. Similarly, Tables 1, 2 and 3 provide support for the 194 residue.

Applicants respectfully request withdrawal of the rejection.

Claims 1, 19, 28, 30-31 and 33-50

Claims 1, 19, 28, 30-31 and 33-50 stand rejected under 35 USC §112, first paragraph as allegedly containing subject which was not described in the specification in such a way as to convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant respectfully traverses.

Although Applicants must respectfully disagree with the Examiner's assertion, in order to further their business interests and prosecution of the present application, yet without acquiescing to the Examiner's arguments, Applicants have amended claims 1, 28, 39 and 42 to recite "consisting essentially of" instead of "comprising". Withdrawal of the rejection is respectfully requested.

Claims 1, 19, 28, 30-31 and 33-50

Claims 1, 19, 28, 30-31 and 33-50 stand rejected under 35 USC §112, first paragraph as failing to be described in the specification. Specifically, the Examiner asserts that the specification does not reasonably provide enablement of all cutinase variants having a substitution corresponding to residues 192, 194, and/or 219 of SEQ ID NO:2. Applicant respectfully traverses.

Applicant must respectfully disagree with the Examiner's argument and rationale that the specification lacks guidance. However, Applicants believe the amendments to Claims 1, 28, 39 and 42 provided for *supra* render this rejection moot as well.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 USC 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

35 U.S.C. §112, second paragraph.

Claims 1, 19, 28, 30-31 and 33-50

Claims 1, 19, 28, 30-31 and 33-50 are rejected under 35 USC §112, second paragraph being indefinite. Specifically, the Examiner asserts the recitation of "wild-type *Pseudomonas mendocina* cutinase" or wild-type *P. mendocina* cutinase" renders the claims unclear. Applicants respectfully traverse.

Definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the art at the time the invention was made. *See, e.g., Atmel Corp. v. Information Storage Devices, Inc.*, 198 F.3d 1374, 53 U.S.P.Q.2d 1225 (Fed. Cir. 1999), "it is well-established that the determination whether a claim is invalid as indefinite 'depends on whether those skilled in the art would understand the scope of the claim when the claim is read in light of the specification.'" quoting *North Am. Vaccine Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 1579 (Fed. Cir. 1993). *See also, Howmedica Osteonics Corp. v. Tranquil Prospects, Ltd.*, 401 F.3d 1367, 1371 (Fed. Cir. 2005), wherein the Federal Circuit overturned an invalidity decision, concluding that "one of ordinary skill in the art would readily ascertain from the written description of the patents that the "transverse sectional dimension" calls for a two-dimensional measurement."

Thus, an important consideration in is whether the terms in a claim adequately define to one skilled in the art the metes and bounds of the claim. Applicants have provided a definition of "wild-type" on page 6, lines 30-31, of the present application. Therefore, Applicants have provided a definition readily understood by the skilled artisan; the claims are definite. Withdrawal of the rejection is respectfully requested.

Claim 19

Claim 19 stands rejected under 35 USC §112, second paragraph as failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner asserts that Claim 19 is confusing because there can be no substitution with Ser at position 219 as Ser is the original residue at that position. Applicants gratefully acknowledge the Examiner's attention to detail. The claims as originally filed had the substitution of Gly for the Ser at position 219. Applicants in their Response filed December 20, 2004 unintentionally amended Claim 19 to (incorrectly) cite the substitution as being Ser not Gly. By the current amendment Applicants have corrected this inadvertent error. Withdrawal of the rejection is respectfully requested.

Claim 49

Claim 49 stands rejected under 35 USC §112, second paragraph as failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner asserts that it is not clear how the variant comprises substitution at position 194 (see page 4 of the Office Action). Applicants respectfully traverse.

Although Applicants must respectfully disagree with the Examiner's assertion, in order to further their business interests and prosecution of the present application, yet without acquiescing to the Examiner's arguments, Applicants have amended the claim to (hopefully) clarify the claim. Withdrawal of the rejection is respectfully requested.

35 U.S.C. §103.

The Examiner has maintained his rejection of claims 1, 28, 30, 33-39 and 41-50 as allegedly obvious over Poulouse, *et al* (US Patent 5,352,594). Applicant respectfully traverses the rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Thus, a *prima facie* case of obviousness requires the Examiner to cite to a combination of references which (a) suggests or motivates one of skill in the art to modify their teachings to yield the claimed invention, (b) discloses the elements of the claimed invention, **and** (c) provides a reasonable expectation of success should the claimed invention be carried out. Failure to establish any one of these requirements precludes a finding of a *prima facie* case of obviousness and, without more, entitles Applicants to withdrawal of the rejection of the claims in issue.[1] Applicants urge that the Examiner has failed to establish at least one of the requirements, i.e., a reasonable expectation of success, as discussed below.

Applicants submit that Poulose *et al.* teach ". . . one would in general use the crystal structure of the enzyme to determine which amino acids are within 15 angstroms of the active site regardless of the primary structure of the enzyme. Where no crystal structure is available, positions in the primary sequence about 6 amino acids on either side of a catalytic amino acid would be within the 15 angstrom requirement." (Poulose *et al.*, at col. 5, lines 50-57). Applicants respectfully submit that as the catalytic triad is composed of Ser126, Asp176, and His206 (*i.e.*, positions 140, 220, and 190 of SEQ ID NO:2), there is no teaching nor suggestion in Poulose *et al.* to modify the amino acid at any of the currently claimed positions in order to increase the polyesterase activity and/or thermostability of the enzyme. The Examiner has acknowledged this assessment (see page 9 of the Office Action).

---

1 *See e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990); and *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

At best Poulouse *et al.* is an invitation to try. The "obvious to try" standard in determining the patentability is a standard which has been thoroughly discredited. Indeed, an obviousness rejection is inappropriate, where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d 894, 903, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); *Merck & Co., Inc. v. Biocraft Laboratories, Inc.*, 10 USPQ2d 1843, 1845 (Fed. Cir. 1989). For example, there is no direction within Poulouse *et al.* as to which, *if any*, amino acid falling within *6 amino acids* on *either* side of *any* one of the *three residues* in the catalytic triad could be replaced with *any* one of the other *19 amino acids* would result in enhanced thermostability and/or polyesterase activity. There is no motivation to select from the (6*2*3*19=) 684 possibilities provided the currently claimed invention.

Under patent law with regard to obviousness, a reasonable expectation of success is to be assessed from the perspective of one of ordinary skill in the art at the time the invention was made. At the time the invention was made it was well established that altering amino acid sequences could result not only in differences in the expression and secretion levels of the protein but also alter the properties of the protein. It was very likely that altering the amino acids in the catalytic region would result in a decrease in the enzymatic activity or thermostability. This supports Applicants' position that one skilled in the art would not have a reasonable expectation of success in altering the amino acid sequence as presently claimed, e.g., creating the variant I192M, would enhanced thermostability and/or polyesterase activity.

Thus, Applicant respectfully requests that this rejection be withdrawn and the Claims be passed to allowance.

CONCLUSION

In light of the above amendments, as well as the remarks, the Applicants believe the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-7615.

Respectfully submitted,
GENENCOR INTL., INC.

Victoria L Boyd

Victoria L. Boyd
Registration No. 43,510

Date: November 14, 2005

Genencor International, Inc.
925 Page Mill Road
Palo Alto, CA 94304
Tel: 650-846-7615
Fax: 650-845-6504

PROTEINS: Structure, Function, and Genetics 23:301–317 (1995)

A Critical Assessment of Comparative Molecular Modeling of Tertiary Structures of Proteins*

Steven Mosimann, Ron Meleshko, and Michael N.G. James
Medical Research Council of Canada, Group in Protein Structure and Function, Department of Biochemistry, University of Alberta, Edmonton, Alberta T6G 2H7, Canada

ABSTRACT In spite of the tremendous increase in the rate at which protein structures are being determined, there is still an enormous gap between the numbers of known DNA-derived sequences and the numbers of three-dimensional structures. In order to shed light on the biological functions of the molecules, researchers often resort to comparative molecular modeling. Earlier work has shown that when the sequence alignment is in error, then the comparative model is guaranteed to be wrong. In addition, loops, the sites of insertions and deletions in families of homologous proteins, are exceedingly difficult to model. Thus, many of the current problems in comparative molecular modeling are minor versions of the global protein folding problem. In order to assess objectively the current state of comparative molecular modeling, 13 groups submitted blind predictions of seven different proteins of undisclosed tertiary structure. This assessment shows that where sequence identity between the target and the template structure is high (> 70%), comparative molecular modeling is highly successful. On the other hand, automated modeling techniques and sophisticated energy minimization methods fail to improve upon the starting structures when the sequence identity is low (~30%). Based on these results it appears that insertions and deletions are still major problems. Successfully deducing the correct sequence alignment when the local similarity is low is still difficult. We suggest some minimal testing of submitted coordinates that should be required of authors before papers on comparative molecular modeling are accepted for publication in journals.

Key words: molecular model, comparative model, homology model, structure prediction, calculated structure

INTRODUCTION

Once a protein's sequence has been determined and it has been found to be a new member of a structurally characterized protein family, it is relatively straightforward to build a molecular model of the protein using a set of simple guidelines.[1,2] Presently, there are several commercial and public domain computer programs that have been developed for modeling; these programs remove much of the tedium from the process. There are numerous reasons for constructing comparative molecular models of proteins. The molecular model may explain the structural basis of existing experimental results and can provide one with structural information on which further experiments can be planned, executed, and evaluated. Site-specific mutations of the gene coding for the specific protein can provide important data regarding the protein's function. Perhaps, some of the most revealing experiments are those designed to predict and to probe the molecular reasons for an enzyme's specificity.[3] On a more practical note, the molecular model can sometimes be used successfully to determine phases for a crystal structure determination using the method of molecular replacement.[4] The more spectacular uses, however, are typified by the recent successful application of comparative molecular modeling for identifying new classes of lead compounds in antimalarial drug development.[5]

An example of the successful prediction of an enzyme's specificity from comparative molecular modeling is that for granzyme B (CCP1), a serine proteinase from cytotoxic T lymphocytes.[3] A molecular model of CCP1 (48% identical to rat mast cell proteinase II) showed that an arginine at position 226 would occupy the S_1 specificity pocket, thereby suggesting a P_1 specificity for an aspartate or glutamate residue. Subsequent synthesis and testing of a series of substrates differing in the nature of the P1 residue confirmed the aspartate specificity of CCP1.[6] The P_1 specificity of CCP1 has recently been altered by site-specific mutagenesis of the residue at

*This assessment does not indicate that any one particular modeling group or modeling technique is superior to any other. We do not believe that comparative molecular models can be ranked using a single or even several numeric indicators. As such, claims that particular modeling techniques are superior based upon the results herein are not justifiable, in our opinion.

Received March 30, 1995; revision accepted June 20, 1995.
Address reprint requests to Michael N.G. James, Medical Research Council of Canada, Group in Protein Structure and Function, Department of Biochemistry, University of Alberta, Edmonton, Alberta T6G 2H7, Canada.

I hereby certify that this correspondence is being sent by facsimile transmission in accordance with § 1.6(d) addressed to Art Unit 1652, Central Facsimile No. (571)273-8300, the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Date: November 14, 2005

By: Aida Martin

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.: 10/091,912 Confirmation No. 9189

Applicant: Bott *et al.*
Filed: March 5, 2002
Art Unit: 1652
Examiner: David J. Steadman
Docket No.: GC724
Customer No.: 5100

PETITION FOR EXTENSION OF TIME

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

The following extension of time is requested to respond to the Office Action dated May 18, 2005:

one month to _____; the extension fee is $120.00.

two months to _____; the extension fee is $450.00.

three months to November 18, 2005; the extension fee is $1,020.00.

four months to _____; the extension fee is $1,590.00.

five months to _____; the extension fee is $2,160.00.

The extended time for response does not exceed the statutory period.

[ ] The shortened statutory period has been reset by an Advisory Action dated _____.

[X] Charge $1,020.00 to Deposit Account No. 07-1048.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 07-1048 (Docket No. GC724). A duplicate of this paper is enclosed.

Respectfully submitted,

Date: November 14, 2005

Victoria L. Boyd
Registration No. 38,230

Genencor International, Inc.
925 Page Mill Road
Palo Alto, CA 94304-1013
Tel: 650-846-4072
Fax: 650-845-6504

I hereby certify that this correspondence is being sent by facsimile transmission in accordance with § 1.6(d) addressed to Art Unit 1652, Central Facsimile No. (571)273-8300, the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Date: November 14, 2005

By: _____
Aida Martin

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No.: 10/091,912 Confirmation No. 9189

Applicant: Bott *et al.*
Filed: March 5, 2002
Art Unit: 1652
Examiner: David J. Steadman
Docket No.: GC724
Customer No.: 5100

PETITION FOR EXTENSION OF TIME

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Sir:

The following extension of time is requested to respond to the Office Action dated May 18, 2005:

one month to _____; the extension fee is $120.00.

two months to _____; the extension fee is $450.00.

three months to November 18, 2005; the extension fee is $1,020.00.

four months to _____; the extension fee is $1,590.00.

five months to _____; the extension fee is $2,160.00.

The extended time for response does not exceed the statutory period.

[ ] The shortened statutory period has been reset by an Advisory Action dated _____.

[X] Charge $1,020.00 to Deposit Account No. 07-1048.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 07-1048 (Docket No. GC724). A duplicate of this paper is enclosed.

Respectfully submitted,

Date: November 14, 2005

Victoria L. Boyd
Registration No. 38,230

Genencor International, Inc.
925 Page Mill Road
Palo Alto, CA 94304-1013
Tel: 650-846-4072
Fax: 650-845-6504